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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,701	03/15/2004	Oron Yacoby-Zeevi	27673	8964

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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,701	YACOBY-ZEEVI, ORON	
	Examiner	Art Unit	
	Kelaginamane T. Hiriyanna	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *1-11 & 18-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restriction of Invention

Applicant's election without traverse of restriction requirement in the reply filed on January 31, 2007 is acknowledged. Applicant elects without traverse the invention Group-III claims 12-17. Applicants further election of species acknowledged.

Claims 12-17 are pending and presently under examination.

Claims 1-11 and 18-37 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected claims, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 01/31/07.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 12-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of the invention encompasses transplantation of any cell and wherein said cell having any extracellular matrix degrading enzymes externally added including any glycosaminoglycan degrading enzymes that enhance in vivo implantations etc of said cell.

At the best the specification only teaches B16-F1 cells having added p60 heparanase and injected into a mouse and enhancing metastases of said cell into the lungs. The applicant further broadly teaches other extracellular matrix degrading enzymes and different cell types that may be enhanced to mobilize for repairing various tissues. However, such a broad guidance to matrix degradative enzymes and cell/tissue types does not constitute the specific direction and guidance the artisan would require to

reasonably predict that any matrix degradative enzymes can be used and any cells can be mobilized etc in vivo.

The specification does not describe sufficient number of examples cell types and/or enzymes used for enhancing extravasation, implantation, transplantation, invasion and or migration of said cells in vivo. Thus the number of examples provided does not commensurate with the scope and breadth of instant claims.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see <http://www.uspto.gov>). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (See In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics.

Since the specification fails to disclose other claimed cells (other than B16-F1 tumor cell) and other externally added purified ECM degrading enzymes (other than said haparanase) that are used for in vivo transplantation with an enhanced extravasation, implantation, transplantation, invasion and or migration of said cells, it is not clear to one of skill in art that any said enzymes can be used and that any cells can be enhanced in implantation etc in vivo. One cannot describe what one has not conceived. (See Fiddes v. Baird, 30 USP2d 1481 at 1483). Therefore, the disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312,*

48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). In the instant case the transplantable cell types enhanced in vivo for extravasation, implantation, transplantation, invasion or migration and the purified ECM degradative enzymes added to said transplantable cells, as has been broadly claimed, are defined only by a statement of a broad function that encompasses any cell that is transplantable and any enzyme that degrades ECM, which conveyed no distinguishing information about the structural and functional identity of the broadly claimed species. Accordingly one of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of a single member of this genus would not be representative of claimed genus of compounds and is insufficient to support the claim in its present scope. At the best the specification provides the description of B16-F1 cells having added p60 heparanase and injected into a mouse and thus enhancing metastases of said cell into the lungs.

Claims 12-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of in vivo cell transplantation of tumor cells in a mouse comprising injecting transplantable cells with added heparanse so as to enhance transplantation, invasion and/or migration of said cells in to the lungs of said mouse, is not enabled for transplantation of any cells or said cells having any adhering purified extra-cellular matrix degrading enzymes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Since the specification fails to disclose, commensurate with the breadth of instant claims, a representative number of enabled examples different transplanted cell types that were enhanced with regard to their extravasation, implantation, transplantation, invasion or migration properties and the use of a sufficient number of examples ECM degrading enzymes for achieving the same, one of ordinary skill in the art would conclude that the invention is unpredictable and would require undue experimentation to practice the invention in its full scope, it is unclear how one skilled in the art use the invention as

claimed (supra). Art is unpredictable with regard to the ECM degrading enzymes that enhance transplantation. For example an increased levels of MMP-9, an ECM degrading enzyme, leads to an acute rejection of the transplant rather than enhancing transplantation (Kuyvenhoven et al Transplantation, 2004, 77(11): 1646-52, Abstract). The applicant's disclosure thus does not enable one skilled in the art to practice the invention as claimed without further undue amount of experimentation, which requires the testing any and/or all ECM degradative enzymes with any and/or all transplantable cell types in order to ascertain which or all of the cell types in combination with what externally added ECM degradation enzymes would enhance said extravasation, etc of said cell types in vivo to bring about an enhanced transplantation of broadly claimed cells. At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 12 and 14 are rejected under 35 USC 102 (b) as being anticipated by Quax et al., (1991, J. Cell. Biol. 115 : 191-199).

The above claims are directed to an in vivo method of cell transplantation of cells provided with a matrix-degrading enzyme that enhances extravasation, implantation, transplantation, invasion or migration of said cells in vivo.

Regarding claims 12 and 14 Quax teaches the metastatic behaviour of a human melanoma cell line in nude mice after treating melanoma cells with externally added

trypsin or expressing uPA (urokinase-type plasminogen activator which adheres to cell surface by binding to a receptor) protease that is transplanted by inoculating subcutaneously into the lateral thoracic wall (p.191, p.193 col.1 paragraphs 2-4). These results indicate that proteases like uPA are involved in the early steps of metastastatic cascade (p.198, col.1, 3rd paragraph). Thus the cited art anticipates the invention as claimed.

Claims 12 and 13 are rejected under 35 USC 102 (b) as being anticipated by Sordat et al (1990, Cell Differ. Dev. 32: 277-285).

The above claims are directed to an in vivo method of cell transplantation of cells provided with a matrix-degrading enzyme that enhances extravasation, implantation, transplantation, invasion or migration of said cells in vivo

Regarding claims 12 and 13 Sordat teaches a gene transfer technique to evaluate the role of uPA in enhancing the expression of the invasive malignant phenotype. Mouse L-cell transfectants expressing human uPA were generated. These tansfectants were tested uing various methods including lung colony formation in vivo. Results from these studies provide direct evidence for an enhancing role of uPA in malignanat invasion and experimental metastasis of uPA (abstract). Thus the cited art anticipates the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15-17 are rejected under 35 USC 103 (a) as being unpatentable over Quax et al., (1991, J. Cell. Biol. 115 (191-199)) applied to claims 12, 14 as above and further in view of Savion et al (1987, J. Cellular. Physiol.. 130: 77-84.

The above claims are directed to an in vivo method of cell transplantation of cells provided with a matrix-degrading enzyme which enhances extravasation, implantation, transplantation, invasion or migration of said cells in vivo

Regarding claims 12 and 14 Quax teaches the metastatic behaviour of a human melanoma cell line in nude mice after treating melanoma cells with externally added trypsin or expressing uPA (urokinase-type plasminogen activator which adheres to cell surface by binding to a receptor) protease that is transplanted by inoculating subcutaneously into the lateral thoracic wall (p.191, p.193 col.1 paragraphs 2-4). These results indicate that proteases like uPA are involved in the early steps of metastastatic cascade (p.198, col.1, 3rd paragraph). Quax however, does not teach the use heparanase in tumor cell metastasis.

Regarding limitation in claim 15-17 Savion teaches the rationale for using heparanase in increasing the cell migration or metastasis. Both activated murine macrophages and different metastatic tumor cells attach invade, penetrate confluent endothelial cell layer by degrading heparin sulfate proteoglycans where heparanase cleaves the said substrate. The macrophages donot store heparanase intracellularly but is instead found pericelularly and requires a continous cell-matrix contact and in B16-BL6 metastatic melanoma cell heparanase also extracellular cell associated enzymes necessary for metastasis (Abstract).

Thus it would have been obvious for one of ordinary skill in the art to substitute heparanase of Savion for the proteases used for extracellular matrix degradation in Quax method for increasing tumor metastasis of injected cells in nude mice. One of ordinary skill in the art would have been motivated to make and use heparanse as proteoglycan degradation is an important and a critical step in mobilizing the cells. One of ordinary skill in the art would have reasonable expectation of success making using heparanase because art at time of instant filing teaches that the ability of normal and malignant blood borne cells to extravasate correlates well with the activity of heparanase. Thus, the claimed invention was *prima facie* obvious.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is ***571 272-0548.*** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach*, may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

Kelaginamane T. Hiriyanna

Patent Examiner

Art Unit 1633

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